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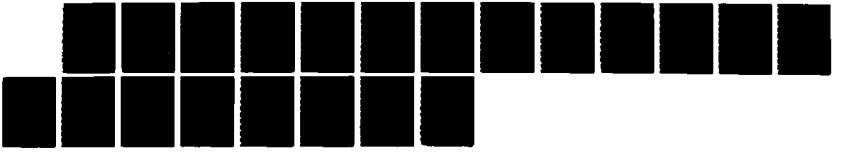

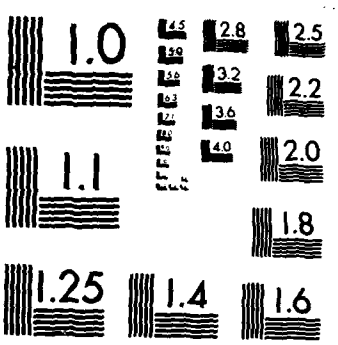

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A STUDY OF THE TOXICITY OF THE METABOLITES OF THE CRUISE MISSILE FUEL JP-10 ON SEVERAL ANIMAL SPECIES

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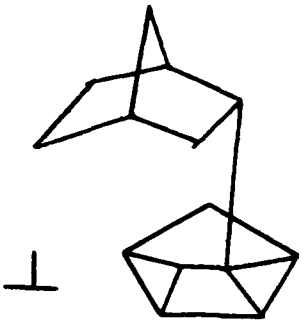
ABSTRACT

Groups of male and female Fischer 344 rats, C-57-BL mice and Syrian Golden hampsters were dosed with 5-hydroxy-JP-10 and 5-keto-JP-10, the metabolites of the cruise missile fuel JP-10, in order to study their toxicity. 5-Hydroxy-JP-10 proved to be an extremely toxic central nervous system depressant. The effects of 5-hydroxy-JP-10 on weight gain appeared to be most pronounced in the male rat. 5-Keto-JP-10, because it is absorbed less readily than 5-hydroxy-JP-10, appeared to be relatively non-toxic. Neither of the JP-10 metabolites produced nephrotoxic effects in the doses administered.

The nephrotoxic effects suffered by male rats exposed to hydrocarbon based fuel systems have led to intense investigations by scientists to determine the etiology of the pathology. Studies conducted to characterize the nephrotoxic activity of unleaded gasoline indicated that the toxic insult occurred predominantly from the fractions containing saturated, branched chain, aliphatic hydrocarbons (1). Recent investigations have shown that branched chain hydrocarbon molecules are not the only hydrocarbon structures capable of eliciting a nephrotoxic effect. For example, 50 male rats exposed one year to the vapors of the single hydrocarbon component fuels RJ-5 (endo-endo-dihydrodinorboradiene) (1) and JP-10 (exo-2,3,3a, 4,5,6,7,7a-octahydro-4,7-methano-1H-indene) (2) resulted in the formation of 9 primary renal cell carcinomas and one poorly differntiated malignant renal neoplasm compared to only one renal cell carcinoma in a control rat group (2).



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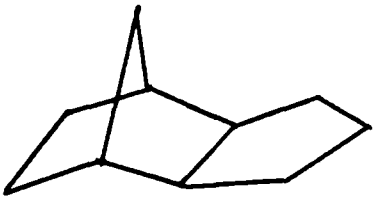

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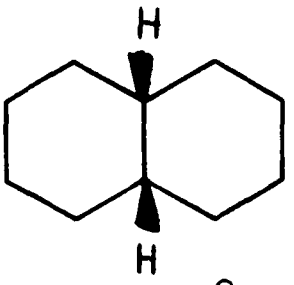
The cyclic hydrocarbons cis-and trans-decalin (3 and 4), components of fuel mixtures, were also demonstrated to be capable of producing kidney lesions in male rats (2). Short term (14 day) exposure of male rats to 3 and 4 by either a gavage or an inhalation route resulted in hyaline droplet formation at the corticomedullary junction of the proximal renal tubules (3). The hyaline droplet accumulation was demonstrated to consist of alpha



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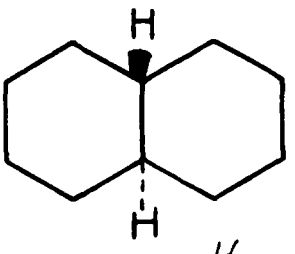

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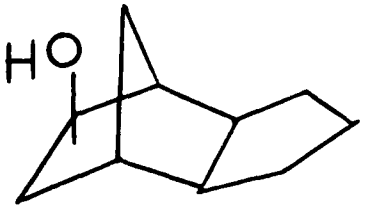
2u globulin, a protein previously identified by Roy and Niehaus (4). Alpha 2u globulin is a low molecular weight protein (18,000-20,000 Daltons) which after synthesis by the liver is filtered through the glomeruli of the kidney. The alpha 2u globulin is then reabsorbed by the proximal convoluted tubules and catabolized by lysosomes into its constituent amino acids. The accumulation of the hyalin droplets in epithelial cells is thus an indication that the proximal tubules can no longer handle the alpha 2u globulin in a normal manner.

It is possible that the parent hydrocarbon may not be the toxic kidney agent, but that a metabolite of the hydrocarbon is the nephrotoxic molecule. Kloss proposed that the interaction of hydrocarbon metabolites with indigneous proteins such as alpha 2u globulin might compromise tubular cell protein catabolism resulting in the kidney lesions observed (5). Indeed, Inman found that 2 was metabolized in male and female Fischer 344 rats to exo-5-hydroxy-JP-10 (5), which was isolated from the urine as the glucuronide conjugate (6). Inman also isolated the ketone metabolite 5-keto-JP-10 (6) from the homogenized kidneys of the male rats dosed with JP-10. The female Fischer 344 rats dosed with JP-10 showed no traces of 6



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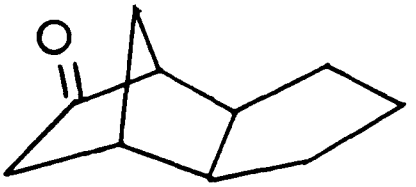

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in their kidneys and also no kidney damage. Olson recently studied the metabolism of 3 and 4 in male and female Fischer 344 rats (7). The results of this study are summarized in Table 1. For both male and female Fischer 344 rats the principal metabolite of cis-decalin was cis,cis-2-decalol and for trans-decalin the major urinary metabolite was trans,cis-2-decalol.

Table 1

URINARY METABOLITES FOUND IN MALE ANF FEMALE FISCHER

344 RATS TREATED WITH CIS - AND TRANS - DECALIN

DECALIN	METABOLITE	RELATIVE ABUNDANCE (GC PEAK AREA)	
		MALE RAT	FEMALE RAT
CIS	Cis,Trans-1-Decalol	2.6	1.0
	Cis,Cis-1-Decalol	1.0	---
	Cis,Cis-2-Decalol	4.0	3.3
TRANS	Trans,Trans-1-Decalol	1.0	---
	Trans,Cis-2-Decalol	5.7	1.0

The difference in metabolism between the male and female rats was that treatment with cis-decalin yielded the metabolite cis,cis-1-decalol in the male rat but not in the female rat.

It was also noted that the metabolite cis,trans-1-decalol, although found in the urine of both male and female rats, was in larger quantities in the male (using the ratio of cis,trans-1-decalol/cis,cis-2-decalol). In the case of trans-decalin, the principal metabolic defference was the presence of the metabolite trans,trans-1-decalol in the male rat urine, and its absence in the female rat urine.

Analysis of kidney extracts from male and female Fischer 344 rats dosed with cis- and trans-decalin also proved interesting. Renal damage was observed in all of the male rats dosed with cis-decalin, and the presence of cis-2-decalone was detected in their homogenized kidney extracts. For the

male rats dosed with trans-decalin, 6 of the 7 rats showed kidney lesions and trans-2-decalone was present in their kidney extracts. The single male rat which presented no renal damage following trans-decalin dosing had no detectable trans-2-decalone in its kidney extract. All of the female Fischer 344 rats dosed with cis- or trans-decalin exhibited no kidney damage and 2-decalone was absent from their kidney extracts. The presence of ketones in the kidneys of the male rats exposed to cyclic hydrocarbons suggests that the ketone is either the causative agent of the renal damage or is a chemical marker indicating the occurrence of renal damage.

To discern whether the hydrocarbon or a metabolite was responsible for the nephrotoxicty found in the male rats, it was proposed that various animal species be treated with 5 and 6, the metabolites of the hydrocarbon fuel JP-10 to see whether either or both of the metabolites were capable of eliciting the hydrocarbon based kidney toxicity. JP-10 was selected as the model compound because there is greater human exposure to the fuel. In addition, the metabolism of JP-10 is less complicated than the decalins.

EXPERIMENTAL

I. Materials

Exo-5-hydroxy-exo-2,3,3a,4,5,6,7,7a-octahydro-4,7-methano-1H-indene (5) was prepared using the procedure of Cristol (8).

5-Keto-exo-2,3,3a,4,5,6,7,7a-octahydro-4,7-methano-1H-indene-6. To a solution of 5 (50 g, 0.32 mole) in 40 ml of glacial acetic acid chilled to 15°C was added a solution of sodium dichromate (30g, 0.10 mole) in 50 ml of glacial acetic acid. The solution was stirred in an ice bath for 30 minutes. The temperature was raised to room temperature and stirring was continued for one hour. Finally, the solution was stirred at 60°C for one hour. Upon cooling 500 ml of water was added. The aqueous solution was extracted 3 times with 200 ml portions of ether. After drying over sodium sulfate, the ether was evaporated. The resulting liquid was distilled yielding 42 g, 0.28 mole of 6, 87% yield, bp 63-5°C (0.2 torr). Anal. Calc. for $C_{10}H_{14}O$: C,79.96; H, 9.39. Found: C, 80.16; H, 9.57.

II. ANIMAL TESTS

Groups of male, female and control Fischer 344 rats, C57-BL mice and Syrian Golden hampsters with 8 animals/group were dosed intragastrically with 0.1 ml - 0.5 ml of 5, 6 or water (control) on an every-other day regimen for 14 days. The animals were placed in metabolism cages for two days after initial dosing so that urine samples could be collected.

During the 14-day dosing period, the animals were weighed daily. At the end of the dosing period, the animals were sacrificed and the livers and kidneys were removed for histopathologic studies. One kidney from each animal was saved for metabolite analysis, commencing with homogenization of the kidney from each individual rat in saline solution. The kidney extraction samples (or urine samples) were then treated with the enzyme mixture beta-glucuronidase/aryl sulfatase (Calbiochem) at 37°C at a pH of 4.0 for 16 hours. Upon cooling to room temperature, the kidney extract or urine sample was then passed through a Clin-Elut column using methylene chloride as the elutent. The analysis scheme is outlined in figure 1. After evaporation, the samples were analyzed using a Hewlett-Packard 5880 gas chromatograph and a Hewlett- Packard 5985 gas chromatograph/mass spectrometer (GC and GC/MS conditions given in figure 2). The identification of metabolites was accomplished by matching GC retention times and MS fragmentation patterns of the metabolites with the GC retention times and MS fragmentation patterns of pure compounds previously prepared.

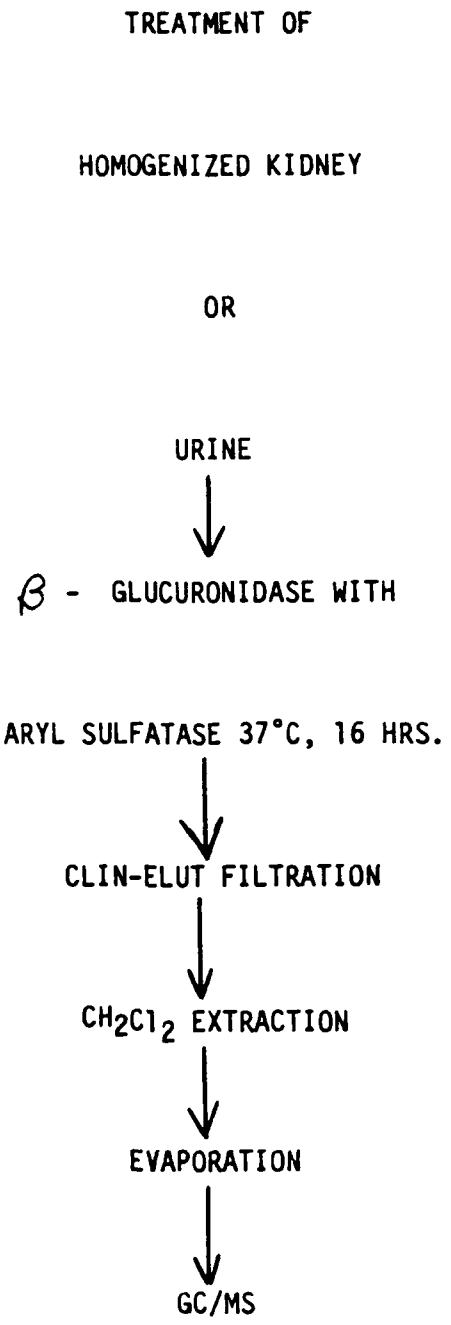
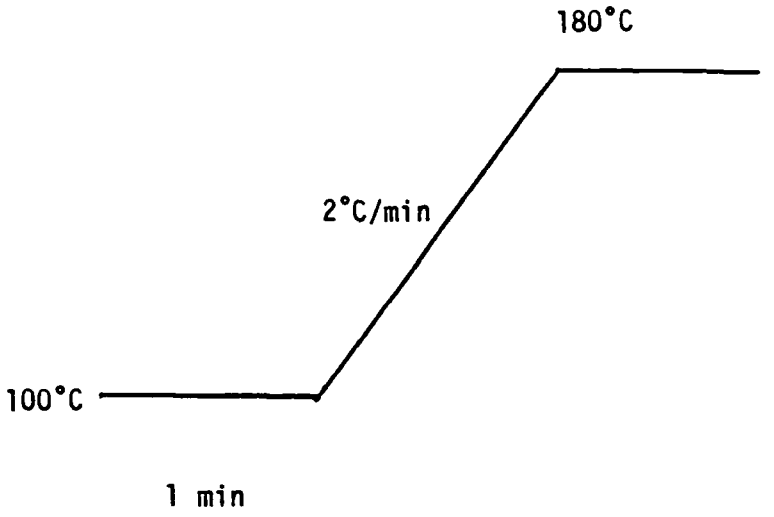


Figure 1. Analysis scheme for rat urine and rat kidney homogenate.

HP 5880 GC

CARBOWAX 20 M CAPILLARY COLUMN 25 m x 0.2 mm ID
LINEAR VOLOCITY 22 cm/sec at 100°C He
FID DETECTOR SPLIT RATIO 5:1 INJECTION PORT TEMPERATURE 200°C



HP 5985 GC/MS

5840 GC
3% SP-1000 4 ft x 2 mm ID GLASS COLUMN
FLOW RATE 28 ml/min He; INJECTION PORT TEMPERATURE 200°C
100/1/10/200/5

MS: QUADRUPOLE. EI MODEL
ELECTRON ENERGY 70 eV
ION SOURCE TEMP 200°C

Figur 2. Gas Chromatography and Gas Chromatography/Mass Spectrometer Conditions for Analysis of Rat Urine.

RESULTS

A. Effect Of Exo-5-Hydroxy-JP-10 (5) On The Weight of Fischer 344 Rats.

The following table list the average weights for rats dosed with either 5 of water (control) for the 14 day exposure period.

Table 2

AVERAGE WEIGHT IN GRAMS OF FISCHER 344 MALE AND FEMALE RATS OVER THE 14 DAY PERIOD. THE RATS WERE DOSED WITH 1 ML/KGM 5 OR WATER ON ODD NUMBER DAYS.

	344 MALE RATS		344 FEMALE RATS	
Day	5 (8 Rats)	Water (8 Rats)	5 (8 Rats)	Water (8 Rats)
1	315	228	199	195
2	307	234	186	180
3	316	237	186	193
4	311	233	196	186
5	316	239	191	188
6	312	242	196	190
7	316	245	194	190
8	309	247	197	190
9	310	248	192	189
10	311	249	193	191
11	311	252	193	191
12	310	253	194	189
13	312	255	192	189
14	314	258	194	191

B. Effect of 5-Keto-JP-10 (6) On The Weight of Male and Female Fischer 344 Rats, C57-BL Mice and Syrian Hamsters.

The following tables list the average weights for male and female animals dosed with either 6 or water (control) for the 14 day exposure period.

Table 3

AVERAGE WEIGHT IN GRAMS OF FISCHER 344 MALE AND FEMALE RATS OVER THE 14 DAY PERIOD. THE RATS WERE DOSED WITH 0.5 mL 6 OR WATER ON ODD NUMBER DAYS.

	344 MALE RATS		344 FEMALE RATS	
Day	5 (8 Rats)	Water (8 Rats)	5 (8 Rats)	Water (8 Rats)
1	322	313	163	163
2	322	316	163	164
3	323	314	166	166
4	316	315	166	167
5	319	316	166	166
6	316	315	166	168
7	318	316	168	169
8	315	313	166	171
9	318	315	168	172
10	315	314	167	170
11	319	317	171	172
12	319	318	170	173
13	321	320	172	174
14	320	319	171	175

Table 4

AVERAGE WEIGHT IN GRAMS OF C57-BL MALE AND FEMALE MICE OVER THE 14 DAY PERIOD. THE MICE WERE DOSED WITH 0.1 mL 6 OR WATER ON ODD NUMBER DAYS.

	344 MALE RATS		344 FEMALE RATS	
Day	5 (8 Rats)	Water (8 Rats)	5 (8 Rats)	Water (8 Rats)
1	18.0	22.4	16.6	18.0
2	17.0	22.5	17.0	17.1
3	17.3	23.0	16.4	17.1
4	17.7	23.3	16.9	16.9
5	20.0	23.1	16.6	17.1
6	19.3	23.9	17.3	17.4
7	20.0	24.0	18.1	17.6
8	20.3	23.6	17.3	17.1
9	20.7	24.0	17.5	17.5
10	21.3	23.4	17.6	17.8
11	20.7	24.0	17.8	18.0
12	21.3	24.0	17.5	18.5
13	20.7	23.3	17.5	18.0
14	20.3	23.3	17.6	18.1

Table 5

AVERAGE WEIGHT IN GRAMS OF SYRIAN GOLDEN MALE AND FEMALE HAMSTERS OVER THE 14 DAY PERIOD. THE HAMSTERS WERE DOSED WITH 0.1 mL 6 OR WATER ON ODD NUMBER DAYS.

	344 MALE RATS		344 FEMALE RATS	
Day	5 (8 Rats)	Water (8 Rats)	5 (8 Rats)	Water (8 Rats)
1	87.1	96.5	95.3	104.3
2	86.8	96.2	95.9	106.1
3	87.6	96.8	98.0	105.9
4	87.9	97.2	97.1	106.7
5	88.1	97.7	98.1	107.9
6	88.4	98.0	98.7	106.8
7	87.7	98.2	100.4	108.7
8	86.1	99.3	98.0	106.1
9	85.9	99.8	100.0	108.6
10	87.2	100.8	101.4	109.7
11	88.1	100.5	102.8	110.5
12	89.9	100.3	103.4	111.7
13	88.2	101.0	107.3	112.1
14	90.1	102.0	103.6	112.3

Table 2 shows that for 5, the weight gain of female fischer 344 rats was not affected relative to the control animals. During the initial dosing period, the female rats did suffer a weight loss which might have been due to eructation of 5 which reduced the appetite. During the second week of dosing, the effect of 5 on weight gain seemed to be reduced.

Table 2 clearly demonstrates the deleterious effect that 5 had upon the weight gain of the male fischer 344 rats relative to controls. During the first week of dosing, 5 caused a significant weight loss. During the second week of dosing, the male rats adjusted to 5 so completely that they nearly regained the weight lost in week 1.

It should be noted that the dose of 5 given to both the male and female Fischer 344 rats was 1 ml/kgm whereas the dose of the JP-10 which produced the lesions was 1.0 ml, a 3-fold difference. When 10 male rats with an average weight of 213 grams were dosed with 1 ml of 5, the rats all died within 48 hours. Male and female C57-BL mice were dosed with 5 in concentrations as low as 0.05 ml/kgm. In every case all the mice died within 15 minutes. Before the mice died, they exhibited severe convulsions indicating that 5 was rapidly affecting the central nervous sytem (CNS). It is well known that some alcohols such as n-butanol and n-pentanol are quite toxic in single doses administered intravenously to rats and mice with LD_{50} ranging from 0.5 g/kgm to 2.3 g/kgm (9). The single intravenous dose LD_{50} for decanol, a C_{10} alcohol like 5, is 6.4 grams/kgm in mice and 12.8 grams/kgm in the rat (10). For every alcohol studied, the CNS was sensitive to the toxic effects of the alcohols. It appears from this study that 5 is 30X more lethal in the rat and at least 60X more lethal in the mouse than many of the common alcohols including the isomeric n-decalol. Table 3, 4 and 5 showed that 6 had no effect on the weight gain in all the animals studied. This indicated that the ketone is readily handled by the body with no irritation to the gastrointestianl tract.

C. METABOLITES

The sole urine metabolite of 5 isolated from both sexes of the Fischer 344 rat, the C57-BL mice and the Golden Syrian hampster was the glucuronic acid conjugate of 5. It appears that all the animals studied have sufficient uridine diphosphate glucuronic acid (UDPGA) and glucuronyl transferase to be able to conjugate 5 as it is absorbed. Many alcohols are excreted in the urine as the glucuronic acid conjugates; thus, the finding of the glucuronic acid conjugate of 5 was not surprising. Based on previous studies, the glucuronic conjugation reaction probably takes place in the liver, although reaction with UDPGA can also occur in the kidney and the gut (11). The short time span that elapsed after the dosing of the mice and their death demonstrates the rapidity with which 5 is absorbed from the gut. Although death did not occur as quickly after dosing in the Fischer 344 rats, the fact that a small quantity of 5 resulted in the death of all the rats indicated that the

glucuronic acid conjugating system could be overloaded rather easily. The excess 5 could then attack the CNS resulting in CNS depression. All the animals survived lower doses of 5 indicating that the glucuronic acid conjugation system was large enough to handle the smaller quantity of 5.

The urine metabolite for 6 found in both sexes in all the animals studied was the glucuronic acid conjugate of 5. Ketones frequently are reduced to the corresponding alcohols by reductase enzyme systems which are distributed widely throughout the body. The fact that the ketone 6 is much less toxic than the alcohol 5 is probably due to the reduced ability of ketones to be absorbed through the gastrointestinal lining relative to alcohols. The hydroxyl group present in the alcohol permits hydrogen bonding to water as well as other biochemical groups. This hydrogen bonding facilitiates the passage of the alcohol through the body's various tissue linings.

There were no traces of any metabolites of JP-10 in the kidneys of all the animals that survived the 14 day dosing regimen as evidenced by gas chromatography/mass spectrometry. This would indicate that the animal body handled the low quantitites of 5 and 6 administered without overloading the kidneys. Hydrogen bonding to water as well as other biochemical groups. This hydrogen bonding facilitates the passage of the alcohol through the body's various tissue linings.

D. HISTOPATHOLOGY

The livers of both sexes of the Fischer 344 rats, the C57-BL mice and the Golden Syrian Hampsters dosed with 5 and 6 were similar to control livers. The kidneys from all the aforementioned animals dosed with 5 and 6 displayed no lesions or hyaline droplet formation. There was no trace of the typical kidney damage exhibited by male Fischer 344 rats exposed to JP-10 and the decalins.

The histopathologic results were not that surprising since it was mentioned in part C that there was no trace of ketone formation in the kidney extracts from any of the animals dosed with 5 or 6. In previous studies the male rats dosed with either JP-10 or the decalins showed kidney damage when a ketone metabolite was isolated from the rat kidney. To speculate as to why neither 5 nor 6 produced kidney damage it is possible that 5, being the precursor of 6, never could reach the kidney in high enough concentration so that the kidney could metabolically oxidize it to the ketone. When attempts were made to elevate the concentration of 5 in both rats and mice, the alcohol caused CNS depression resulting in the death of the animal before kidney damage could occur. An explanation as to the inactivity of the ketone 6 is that 6 is so slowly absorbed from the gastrointestinal tract that it is metabolically reduced to 5 before it can reach the kidney.

A possible experiment to test whether the ketone 6 is the nephrotoxic agent would be to inject 6 directly into the kidney via the renal artery. An attempt to accomplish the above experiment was not completed because the renal artery of the Fischer 344 rats was to narrow to accept a catheter.

C. CONCLUSIONS

The JP-10 metabolite 5 is an extremely toxic chemical. It exerts its lethal effect by severly depressing the central nervous system. 5 is excreted in the urine unchanged.

The JP-10 ketone metabolite 6 is reduced to 5 and excreted in the urine. Compound 6 is not nephrotoxic when administered orally.

Ketone 6 may be nephrotoxic if it can be administered directly to the kidney.

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